PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
PO352PCT/MCG/TD		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/003339	01.10.2004	07.10.2003

International Patent Classification (IPC) or national classification and IPC

C07K14/29, C12N15/31, C07K16/12, A61K39/02, A61K39/295

Applicant

THIRY, Michel et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.05.2005	23.09.2005

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Heiduschat, C

Telephone No. +49 89 2399-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

10/574639
International application No.
PCT/IB2004/003339

IAP20 Rec'd PCT/PTO 31 MAR 2006

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-91	as originally filed
Claims, Numbers	
1-42	as originally filed
Drawings, Sheets	
1/2-2/2	as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,4,5,7,9-13,15-17,20-36,38-41
	No:	Claims	2,3,6,8,14,18,19, 37, 42
Inventive step (IS)	Yes:	Claims	none
	No:	Claims	1-42
Industrial applicability (IA)	Yes:	Claims	1-30,37-41; no opinion for 31-36, 42
	No:	Claims	none

2. Citations and explanations (Rule 70.7):

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, Item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.

PCT/IB2004/003339

Re Item II

Priority

Claim 17 of the present application is directed to a deposited Yersinia strain (BCCM accession No. LMG P-22511). The subject-matter of claims 22 to 36 is also based on said strain. In view of the description this strain was only deposited between the priority date and the filing date (see page 15, l.16 to 17). Thus, any subject-matter based on this strain cells does not enjoy priority rights.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 01/68865 A (AQUA HEALTH LIMITED; SIMARD, NATHALIE; BROUWERS, HUUB; JONES, SIMON;) 20 September 2001 (2001-09-20)

D2: LEONG J C ET AL: "FISH VACCINE ANTIGENS PRODUCED OR DELIVERED BY RECOMBINANT DNA TECHNOLOGIES" DEVELOPMENTS IN BIOLOGICAL STANDARDIZATION, KARGER, BASEL, CH, vol. 90, 1997, pages 267-277, XP001062656 ISSN: 0301-5149

D3: VALENZUELA PDT ET AL.: "Sequence and applications of the Piscirickttsia salmonis genome" BIOLOGICAL RESEARCH, [Online] vol. 34, no. 3-4, 2001, pages R-17, XP002325385 ISSN: 0716-9760 Retrieved from the Internet: URL:http://www.scielo.cl/scielo.php?script=sci_arttext&pid=S0716-97602001000300012&l ng=en&nrm=iso> [retrieved on 2005-04-14]

D4: WO 02/38770 A (THE UNIVERSITY COURT OF THE UNIVERSITY OF ABERDEEN; MELVIN, WILLIAM, T) 16 May 2002 (2002-05-16)

D5: MIQUEL ALVARO ET AL: "Immunoresponse of Coho salmon immunized with a gene expression library from Piscirickettsia salmonis." BIOLOGICAL RESEARCH, vol. 36, no. 3-4, 2003, pages 313-323, XP002325386 ISSN: 0716-9760; cited as P document

D6: WILHELM VIVIAN ET AL: "The complete sequence of the mitochondrial genome of the Chinook salmon, Oncorhynchus tshawytscha." BIOLOGICAL

RESEARCH, vol. 36, no. 2, 2003, pages 223-231, XP009046676 ISSN: 0716-9760

D7: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 2002, HENRIQUEZ V B ET AL: "Improved purification of the obligate intracellular bacteria Piscirickettsia salmonis by iodixanol density gradient centrifugation" XP002325615 Database accession no. PREV200200597234

D8: HENRIQUEZ VITALIA ET AL: "An alternative efficient procedure for purification of the obligate intracellular fish bacterial pathogen Piscirickettsia salmonis." APPLIED AND ENVIRONMENTAL MICROBIOLOGY, vol. 69, no. 10, October 2003 (2003-10), pages 6268-6271, XP001206212 ISSN: 0099-2240

D9: RUESSMANN HOLGER ET AL: "Attenuated Yersinia pseudotuberculosis carrier vaccine for simultaneous antigen-specific CD4 and CD8 T-cell induction." INFECTION AND IMMUNITY, vol. 71, no. 6, June 2003 (2003-06), pages 3463-3472, XP002325391 ISSN: 0019-9567

1. Lack of Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 2, 3, 6, 8, 14, 18, 19, 37 and 42 is not new in the sense of Article 33(2) PCT.

1.1 The present application is based on the cloning of the full sequence of the surface antigen p45 of Piscirickettsia salmonis which may be used for vaccination of fish against salmonid rickettsial septicemia (SRS).

1.2 The document D1 discloses the sequences of several surface antigens of P. salmonis, among others the 30 N-terminal amino acids of mature p45 (Fig. 7; p 7 to 8). The document suggests to use said antigens or the nucleic acids coding therefore for the preparation of vaccines against infection by Piscirickettsia salmonis.
Thus, D1 is considered novelty-destroying to any claim based on a fragment of p45, i.e. claims 2, 3, 6, 8, 14, 18 and 19.

1.3 Claims 37 and 42 are directed to a vaccine and a method of vaccination, respectively, to protect a non-human animal against intracellular pathogen comprising recombinant enteric bacterium that encodes a surface antigen of the intracellular pathogen. The use of such recombinant enteric bacteria for vaccination against disease caused by intracellular pathogens is known in the art, e.g. the use of Y. pseudotuberculosis

expressing an antigen of Listeria monocytogenes is disclosed by D9 (p.3463, l. 1 to p.3464, left column, paragraph 2; p.3469, left column, 2nd paragraph to p.3470 right colimn 3rd paragraph).

Thus, the subject-matter of claims 37 and 42 cannot be considered novel over the prior art.

2. Lack of inventive step

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 4, 5, 7, 9 to 13, 15 to 17, 20 to 36, 38 to 41 does not involve an inventive step in the sense of Article 33(3) PCT.

2.1 In view of the above objections for lack of novelty raised to subject-matter based on fragments of p45 claims 10 to 13, directed to host cells and methods of recombinant production cannot be considered inventive, because they do not comprise any additional technical feature justifying an inventive step.

2.2 In view of the above discussed objections for lack of novelty raised to subject-matter of claim 37 based on a vaccine comprising a recombinant enteric bacteria the subject-matter of claims 38 to 41 cannot be considered inventive in view of D9, as they do not comprise any futher technical feature justifying an inventive step. See also item 2.5.

2.3 Claim 1 is directed to the p45 protein of P. salmonis comprising either the sequence of the mature protein (SEQ ID NO:4) comprising a conservative amino acid substitution or an amino acid sequence that has at least 70 % identity with the amino acid sequences of SEQ ID NO: 2 (prosequence including signal sequence) or SEQ ID NO: 4. Claim 7 is directed to the encoding nucleic acid sequences (SEQ ID NOs:1 and 3).

The document D1 is regarded as being the closest prior art to the subject-matter of claims 1 and 7, and discloses a partial sequence of P. salmonis antigen p45. The subject-matter of claims 1 and 7 therefore differ from D1 in disclosing the full amino acid sequence and the encoding DNA sequence of p45.

The problem to be solved by the present invention may therefore be regarded as the provision of the full sequence of the P. salmonis antigen p45. The solution proposed in claim 1 and 7 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons: The provision of the full-length DNA or amino acid sequence of a protein which had already been partially

sequenced cannot be regarded as inventive. The skilled person would regard it a routine procedure to derive suitable primers in order to clone the full DNA sequence. D6 to D8 describe the purification P. salmonis and the isolation of its genomic DNA. D5 (cited as P-document) discloses that based on said purification method a genome library can be constructed. D3 and D6 mention that the genome of P. salmonis has been sequenced. Thus, in view of D1 in combination with any of D6 to D8 it appears a routine procedure to provide the full-length sequence of p45.

Thus, unless the Applicant can convincingly show, that in this case the cloning of the full sequence was extremely difficult, the subject-matter of claim 1 and 7 does not involve an inventive step and does not satisfy the criterion set forth in Articles 52(1) and 56 EPC.

2.4 The same reasoning applies to claims 4, 5 and 9 which refer to said full length sequence and which do not comprise any additional technical feature justifying an inventive step.

2.5 Claims 15 to 17 and 20 to 24 are directed to Yersinia ruckeri cells encoding the P. salmonis antigen p45 or the antigen comprised in the Y. ruckeri strain according to claim 17, or to a vaccine comprising said recombinant Yersinia ruckeri cells. Claim 41 is directed to a vaccine and its use based on recombinant Y. ruckeri encoding the surface antigen of any intracellular fish pathogen.

It is known from the prior art (see e.g. D9; D2: p.270, l.10-16;p.272, 3rd paragraph) that antigens can be expressed in bacterial hosts that may also act as vaccines themselves. This has also been suggested for Y. ruckeri, which was transfected with an E. coli plasmid vector expressing an IPNV protein (see D2, p.270, l.10 to 16; Table 1). Thus it is considered a routine design option to use recombinant Y. ruckeri as vaccine strain for any fish pathogen. Unless the expression of P. salmonis or other antigens in Y. ruckeri proved extremely difficult the subject-matter of claims 15 to 17, 20 to 24 and 41 cannot be considered inventive.

2.6 The combination of P. salmonis antigens with known antigens of IPNV (see D4) or A. salmonicida as in claims 25 to 30 can also not be considered inventive, because multivalent vaccines are known in the art (e.g. D4: Example 8, p.34 to 35).

2.7 The same reasoning as discussed in items 2.5 and 2.4 applies to claims 31 to 36 which are directed to methods of protecting a fish using above discussed vaccines.

3. Industrial Applicability

Claims 31 to 36 and 42 are directed to methods of medical treatment.
For the assessment of said claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.